The Manganese-Catalyzed Cross-Coupling Reaction and the Influence of Trace Metals

Santilli, Carola; Beigbaghlou, Somayyeh Sarvi; Ahlburg, Andreas; Antonacci, Giuseppe; Fristrup, Peter; Norrby, Per-Ola; Madsen, Robert

Published in:
European Journal of Organic Chemistry

Link to article, DOI:
10.1002/ejoc.201701005

Publication date:
2017

Document Version
Peer reviewed version

The Manganese-Catalyzed Cross-Coupling Reaction and the Influence of Trace Metals

Carola Santilli,[a] Somayyeh Sarvi Beigbaghlou,[a,b] Andreas Ahlburg,[a] Giuseppe Antonacci,[a] Peter Fristrup,[a] Per-Ola Norrby,[c,d] and Robert Madsen*[a]

Abstract: The substrate scope of the $MnCl_2$-catalyzed cross-coupling between aryl halides and Grignard reagents has been extended to several methyl-substituted aryl iodides by performing the reaction at elevated temperature in a microwave oven. A radical clock experiment revealed the presence of an aryl radical as an intermediate leading to the proposal of an $S_{RN}1$ pathway for the coupling. The mechanistic information gave rise to suspicion about two previously published cross-coupling reactions catalyzed by manganese(II) salts. As a result, the coupling between aryl halides and organostannanes as well as between aryl halides and amines were revisited. Both reactions were found impossible to reproduce without the addition of small amounts of palladium or copper and are therefore not believed to be catalyzed by manganese.

Introduction

Manganese is one of the most abundant and cheapest metals in the periodic table. Manganese is also present in all living systems and constitutes a relatively non-toxic metal.[1] A significant number of manganese-catalyzed homogeneous reactions have therefore been developed over the past decade in order to replace the expensive and toxic platinum group metals in the same reactions or to develop entire new transformations.[2] This is also true for the manganese-catalyzed cross-coupling reaction to form C-C and C-N bonds where manganese(II) salts have been employed as the catalysts. Progress, however, has been slower in the development of these transformations and some reactions are poorly understood.

Several groups have studied the $MnCl_2$-catalyzed cross-coupling between Grignard reagents and vinyl/aryl halides.[3] The reactions are carried out in THF solution with 3 – 10% of $MnCl_2$ at a temperature between 0 °C and rt.[3] Very recently, we investigated the substrate scope in detail for the coupling with aryl halides and showed that the reaction was limited to aryl chlorides with cyano or ester groups in the *para* or *ortho* position.[3a] The Grignard reagent, on the other hand, could be either an aryl- or an alkylmagnesium halide.[3a] The mechanism was also investigated by a radical clock experiment where an aryl radical was identified as an intermediate leading to the proposal of an overall $S_{RN}1$ pathway for the coupling.[3a] Besides the reaction with Grignard reagents, aryl halides have also undergone substitution with other groups in the presence of manganese catalysts. Aryl and vinyl iodides have been coupled with aryl, vinyl and alkynyl tributylstannanes in the presence of $MnBr_2$.[4] Furthermore, aryl halides have been coupled with aryl boronic acids and alkyl acrylates in the presence of manganese deposited on heterogeneous supports although the actual catalysts are less well defined in these cases.[5] In addition to C-C bond formation C-N bonds have also been formed where $MnCl_2$ has been presented as a catalyst for connecting aryl halides and amines.[6]

A constant concern in the development of catalytic reactions with new metals is the possible presence of trace amounts of other metals which may then be the actual catalyst for the transformation.[7] For the cross-coupling reaction minute quantities of palladium or copper impurities have in some cases been responsible for a transformation which was otherwise believed to be either metal free or catalyzed by a different metal.[8]

Herein, we describe our further development of the $MnCl_2$-catalyzed coupling between aryl halides and Grignard reagents. The substrate scope in the halide has been extended beyond cyano- and ester-activated substrates by performing the reaction at elevated temperature in a microwave oven. In addition, we describe our attempts to reproduce two previously published manganese-catalyzed coupling reactions[4,6] where we believe trace amounts of other metals serve as the actual catalyst.

Results and Discussion

Bromobenzene and *p*-tolylmagnesium bromide in THF solution were selected as the substrates in a 1:2 ratio for the initial studies with 10% of $MnCl_2$ since no cross-coupling occurred in this case at room temperature or upon refluxing the reaction mixture.[3a] However, heating the solution in a microwave oven at 180 °C produced the desired heterocoupling product in 40% yield with homocoupling of the Grignard reagent and

[a] C. Santilli, S. S. Beigbaghlou, A. Ahlburg, G. Antonacci, P. Fristrup, R. Madsen
Department of Chemistry
Technical University of Denmark
2800 Kgs. Lyngby (Denmark)
E-mail: rm@kemi.dtu.dk
http://www.kemi.dtu.dk
[b] S. S. Beigbaghlou
Faculty of Chemistry
Kharazmi University of Tehran (Tarbiat Moalem University)
49 Mofateh Avenue, Tehran 15719 (Iran)
[c] P.-O. Norrby
Department of Chemistry and Molecular Biology
University of Gothenburg
Kemigården 4, 412 96 Göteborg (Sweden)
[d] P.-O. Norrby
Pharmaceutical Sciences
AstraZeneca
Pepparedsleden 1, 431 83 Mölndal (Sweden)

Supporting information for this article is given via a link at the end of the document.

dehalogenation of the halobenzene as the major side reactions (Table 1, Entry 1). Increasing or decreasing the temperature gave slightly lower yields (Entries 2 – 5) and the same was observed when $MnCl_2$ was replaced with MnF_2, $MnBr_2$ and MnI_2 (Entries 6 – 8). With one equivalent of $MnCl_2$ the coupling yield increased to 49% at 160 °C (Entry 9).

Since dehalogenation is the major side reaction, the cross-coupling was also investigated with *p*-bromotoluene and phenylmagnesium bromide. The latter is now prepared in Et_2O and initially no improvement was observed in the yield (Entry 10). However, increasing the concentration of the Grignard reagent from 1 M to 3 M raised the yield to 60 – 70% depending on the temperature and the reaction time (Entries 11 – 14). A similar result was obtained when the same concentration of the Grignard reagent in 2-methyltetrahydrofuran (2-MeTHF) was used (Entry 15), which underlines the importance of the concentration to suppress the dehalogenation. The Schlenk equilibrium in Et_2O favors the monomeric ArMgX while Ar_2Mg + MgX_2 becomes more preferred in THF.[9] However, the Schlenk equilibrium can shift very fast and is therefore not believed to be responsible for the different reactivities in THF and Et_2O. Notably, 4% of 4,4'-dimethylbiphenyl was also formed in entry 13 arising from homocoupling of the aryl halide. In the other entries small traces of this homocoupling product was also observed, but it was not further quantified. Replacing *p*-bromotoluene with *p*-iodotoluene gave an additional improvement in the outcome while *p*-chlorotoluene resulted in a lower yield (Entries 16 and 17). A control experiment without $MnCl_2$ gave no conversion of the starting materials and as a result no cross-coupling, dehalogenation and homocoupling were observed (Entry 18). Similarly, no cross-coupling occurred when an aryl triflate was treated with a Grignard reagent under the reaction conditions. Consequently, a 3 M solution of the Grignard reagent in Et_2O and a temperature of 120 °C were selected for general use since it affords a reasonable reaction time in the microwave oven (Entry 13). For comparison, the experiment in Entry 13 was also performed by conventional heating in an oil bath overnight which resulted in 62% yield of 4-methylbiphenyl (Entry 19).

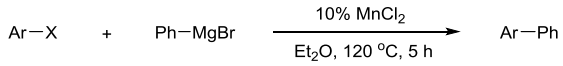
Table 1. Optimization of $MnCl_2$-catalyzed cross-coupling.[a]

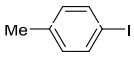
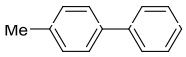
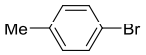
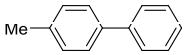
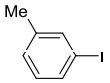
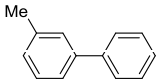
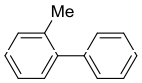
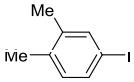
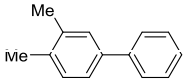
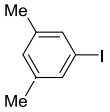
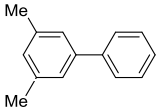
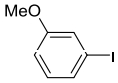
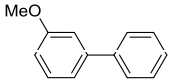
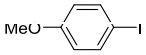
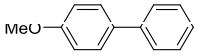
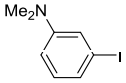
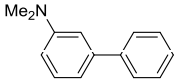
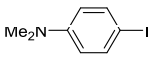
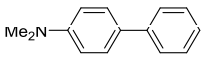
Entry	R	R'	Solvent	*T* [°C]	t [h]	Yield [%][b]
1	H	Me	THF	180	2	40
2	H	Me	THF	200	1	29
3	H	Me	THF	160	2	33
4	H	Me	THF	140	2	34
5	H	Me	THF	120	14	21
6[c]	H	Me	THF[d]	160	2	10
7[e]	H	Me	THF[d]	160	2	29
8[f]	H	Me	THF[d]	160	2	28
9	H	Me	THF[d]	160	2	49
10	Me	H	Et_2O[d]	160	1	23
11	Me	H	Et_2O[g]	160	1	60
12	Me	H	Et_2O[g]	140	2	57
13	**Me**	**H**	**Et_2O[g]**	**120**	**5**	**70[h]**
14	Me	H	Et_2O[g]	100	12	69
15	Me	H	2-MeTHF[g]	160	2	65
16[i]	**Me**	**H**	**Et_2O[g]**	**120**	**5**	**75**
17[j]	Me	H	Et_2O[g]	120	5	33
18[k]	Me	H	Et_2O[g]	120	5	0
19[l]	Me	H	Et_2O[g]	120	18	62

[a] Conditions: aryl bromide (2 mmol), arylmagnesium bromide (4 mmol), $MnCl_2$ (0.2 mmol), decane (1 mmol, internal standard) and solvent (8 mL, i.e. Grignard concentration 0.5 M) in a closed vial with microwave heating. [b] GC yield. [c] With MnF_2 instead of $MnCl_2$. [d] 4 mL solvent (Grignard concentration 1 M). [e] With $MnBr_2$ instead of $MnCl_2$. [f] With MnI_2 instead of $MnCl_2$. [g] 1.3 mL solvent (Grignard concentration 3 M). [h] 4,4'-Dimethylbiphenyl (4%) was also formed. [i] With *p*-iodotoluene. [j] With *p*-chlorotoluene. [k] Without $MnCl_2$. [l] Performed in an oil bath.

With the optimized procedure available the substrate scope could now be explored in further detail with different aryl bromides and iodides (Table 2). 4-Methylbiphenyl was isolated in 66% yield from the reaction between *p*-iodotoluene and phenylmagnesium bromide (Entry 1). Dehalogenation of the aryl iodide was responsible for the remaining conversion of the starting halide. With *p*-bromotoluene as the aryl halide the yield of 4-methylbiphenyl decreased to 47% (Entry 2). *m*-Iodotoluene afforded 3-methylbiphenyl in 50% yield (Entry 3) while the same reaction with *m*-bromotoluene only gave about 20% yield (result not shown). This again illustrates the lower yield with the aryl bromide as compared to the aryl iodide. *o*-Iodotoluene furnished the cross-coupling product in 34% yield (Entry 4) with dehalogenation of the starting material as the main side reaction. Aryl iodides with two methyl substituents in the *meta* and/or *para* position gave the corresponding biphenyl compounds in 77% and 62% yield (Entries 5 and 6). Lower yields were obtained with methoxy and dimethylamino groups in the *meta* or *para* positions due to dehalogenation of the aryl halide (Entries 7 – 10). *p*-Chloroiodo- and *p*-fluoroiodobenzene were also reacted with phenylmagnesium bromide, but only about 10% of the desired biphenyl compounds were obtained in these two cases (result not shown). Very small traces of the homocoupling product from the aryl halide were detected in several entries, but not further quantified. The studies show that aryl iodides are the preferred coupling partners and decent yields can be obtained with simple methyl substituted substrates while other substituents afford lower yields.

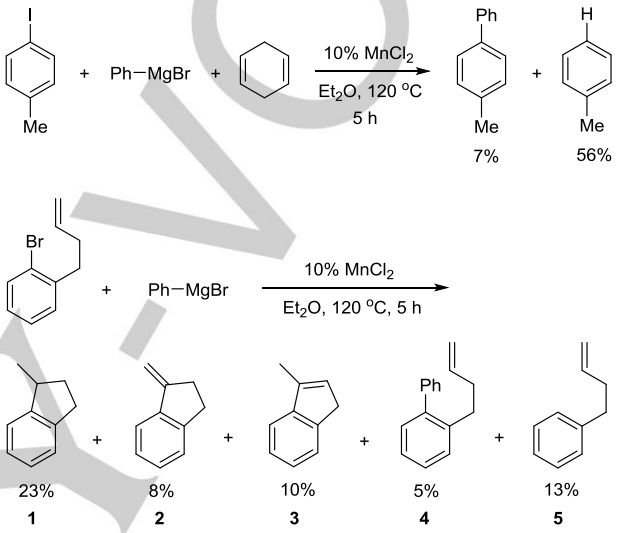
Table 2. Cross-coupling with different aryl halides.[a]



Entry	Ar–X	Ar–Ph	Yield [%][b]
1			66[c]
2			47[c]
3			50[c]
4			34[c]
5			77
6			62[c]
7			26
8			23
9			33
10			28

[a] Conditions: aryl bromide (2 mmol), phenylmagnesium bromide (4 mmol), $MnCl_2$ (0.2 mmol), and Et_2O (1.3 mL, i.e. Grignard concentration 3 M) in a closed vial with microwave heating at 120 °C for 5 h. [b] Isolated yield. [c] Yield based on NMR since isolated product not completely pure.

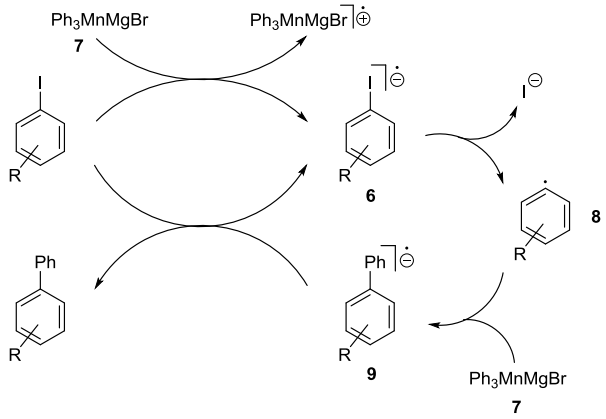
The substrate scope does not provide any information about the mechanism, but based on our recent analysis of the coupling with chlorobenzonitriles,[3a] the reaction may proceed by a radical pathway. In fact, the small amounts of a homocoupling product from the aryl halide may result from dimerization of an intermediate aryl radical. Therefore, two experiments were conducted in order to trap this radical. First, the coupling in Table 1, Entry 16 was repeated in the presence of 10 equiv. of cyclohexa-1,4-diene (Scheme 1). This afforded 4-methylbiphenyl in only 7% GC yield while the dehalogenation product was now obtained in 56% yield. The substantial dehalogenation in the presence of the 1,4-diene indicates the involvement of an aryl radical. To trap this species with an olefin 4-(2-bromophenyl)-but-1-ene was reacted with phenylmagnesium bromide under the optimized conditions (Scheme 1).[10] The reaction gave a mixture of the cyclization products **1** – **3** in a combined yield of 41%. In addition, the cross-coupling product **4** and the dehalogenation product **5** were obtained in 5% and 13% yield, respectively. Again, the results provide a strong indication for the involvement of an aryl radical. The formation of olefins in radical clock experiments has previously been observed and depends on the ease by which the generated radicals are trapped by the solvent.[11]



Scheme 1. Aryl radical trapping experiments.

These results lead to the proposal of the same $S_{RN}1$ mechanism as in our previous cross-coupling with chlorobenzonitriles (Scheme 2).[3a] The reaction is initiated by single electron transfer to the aryl halide to afford radical anion **6** and the most likely one electron donor is the triphenylmanganate complex **7** which is a known radical initiator[12] and is readily formed from $MnCl_2$ and phenylmagnesium bromide.[13] The Grignard reagent appears to be unable to initiate the reaction since the direct cross-coupling between an aryl halide and an arylmagnesium halide was shown to proceed without the formation of an aryl radical.[14] Subsequent loss of the halide furnishes the aryl radical **8** which upon reaction with an aryl nucleophile gives rise to the biphenyl radical anion **9**. The Grignard reagent and the triphenylmanganate complex **7** can both serve as the aryl nucleophile where the latter is a softer nucleophile than the former.[13] The triphenylmanganate complex is the most likely nucleophile since a Grignard reagent has never been shown to react with an aryl radical. Final single electron transfer from the radical anion **9** to the starting aryl halide closes the catalytic cycle. The high temperature is most likely required in the present case since the electron-donating substituents destabilize radical anion **6** and make aryl radical **8** less electrophilic[15] as opposed to the electron-withdrawing substituents in our earlier study.[3a] For the same reason, the homocoupling product from the aryl halide and the

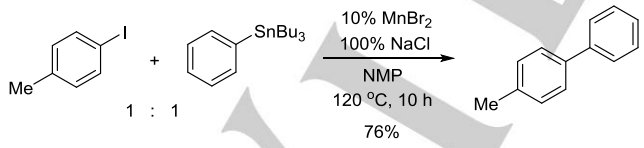
dehalogenation product with cyclohexa-1,4-diene were observed in the present investigation and not in our previous study.[3a]



Scheme 2. Proposed mechanism for $MnCl_2$-catalyzed cross-coupling.

The discovery of a radical pathway in these $MnCl_2$-catalyzed couplings made us revisit two previously published procedures for manganese-catalyzed cross-couplings. In 1997 a $MnBr_2$-catalyzed method was presented for coupling of aryl iodides and arylstannanes[4] while in 2009 – 2012 three papers described the $MnCl_2$-catalyzed condensation between aryl halides and amines.[6] No mechanistic information was presented in any of these publications and based on the reactants and the conditions it appeared doubtful that radical pathways were involved. Consequently, we decided to repeat the experiments in these publications in an attempt to understand the puzzling reactivity.

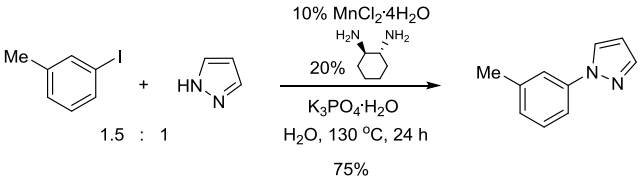
The coupling between aryl iodides and –stannanes was described to take place under the conditions shown in Scheme 3 where the addition of one equivalent of NaCl was essential (although it could be replaced with KCl).[4] The coupling was reported to give a lower yield with $MnCl_2$ while no coupling was observed with MnI_2 or when using aryl bromides or triflates as substrates.[4] No information was provided about the purity of the reagents that were used to carry out these reactions.[4]



Scheme 3. Reported $MnBr_2$-catalyzed coupling between aryl halides and -stannnes.[4]

When we repeated the experiment in Scheme 3 under the exact same conditions we observed no conversion of the aryl iodide and no formation of 4-methylbiphenyl. The coupling in Scheme 3 was also reported to give 81% yield with 10% of CuI as a catalyst instead of $MnBr_2$.[4] Again, we detected no conversion of *p*-iodotoluene when we carried out the transformation with CuI. The experiments with $MnBr_2$ and CuI were performed several times, but the results were the same. The employed solvent, reactants and metal salts were analyzed by inductively coupled plasma mass spectrometry (ICP-MS) which showed the presence of several metal impurities such as lead, mercury and chromium. However, palladium and nickel were not identified in any of the samples beyond the detection limit, *i.e.* 1 ppm for Pd and 5 ppm for Ni. No conversion of the iodide occurred when the reaction in Scheme 3 was carried out with 10% of $NiCl_2$ instead of $MnBr_2$. However, with 10% of $Pd(OAc)_2$ the coupling proceeded to give 4-methylbiphenyl in 52% GC yield together with the two homocoupling products. Several experiments were then performed with lower amounts of $Pd(OAc)_2$ and even with 0.003% of $Pd(OAc)_2$ was it possible to obtain 42% yield of the cross-coupling product. Lowering the amount further to 0.0004% of $Pd(OAc)_2$, however, resulted in no conversion of the aryl halide. Consequently, we do not believe the reported cross-coupling reaction[4] is catalyzed by $MnBr_2$ or CuI, but instead it may be mediated by very small amounts of palladium in the starting materials.

The coupling between aryl halides and amines was described to take place in either DMSO or water with 5 – 20% of $MnCl_2$ as the catalyst and a temperature of 130 – 135 °C.[6] *Trans*-1,2-diaminocyclohexane or proline was employed as the ligand and a base (Cs_2CO_3, K_3PO_4 or NaO*t*Bu) was also added.[6] Regioisomeric products resulting from a benzyne intermediate were reported with NaO*t*Bu as the base[6b] while no regioisomers were disclosed with Cs_2CO_3 or K_3PO_4.[6a,c] $MnCl_2$ of either >99% or 99.99% purity was used in the published reactions,[6] but no analysis for trace elements was performed on any of the components in the transformations. We selected the coupling between *m*-iodotoluene and pyrazole for our experiment since the reaction was reported to give 75% yield under the conditions in Scheme 4[6c] and it would be possible to pinpoint a possible benzyne intermediate in this case.



Scheme 4. Reported $MnCl_2$-catalyzed coupling between aryl halides and amines.[6c]

We repeated the experiment in Scheme 4 under the exact same conditions and with redistilled substrates, ligand and deionized water. The yield of 1-(*m*-tolyl)-1H-pyrazole was 6 – 8% in our hands depending on the source of $MnCl_2$ and with unreacted starting materials remaining. No isomers of the product were formed which excludes an aryne pathway. Interestingly, the yield increased to 45% when deionized water was replaced with ordinary and undistilled tap water. When the reaction in Scheme 4 was done in the absence of $MnCl_2$ (and with deionized water) the yield of 1-(*m*-tolyl)-1H-pyrazole decreased to 2 – 3%. These experiments indicate that $MnCl_2$ is

not able to catalyze the coupling between aryl halides and amines, but instead traces of another element is most likely responsible for the transformation. It has previously been shown that 0.01% of $CuCl_2$ is able to catalyze the coupling between iodobenzene and pyrazole in 88% yield under very similar conditions.[16] In fact, when we performed the reaction in Scheme 4 with 0.01% of $CuCl_2$•H_2O instead of $MnCl_2$, the yield of 1-(*m*-tolyl)-1H-pyrazole increased to 78% while 29% was obtained with a 0.001% loading of $CuCl_2$•H_2O. The solvent and the reactants were again analyzed by ICP-MS, but no copper impurities were found beyond the detection limit which was 20 ppm for $MnCl_2$, 0.02 ppm for *m*-iodotoluene and K_3PO_4, and 0.005 ppm for pyrazole, deionized water and the ligand. Pyrazole, although, contained 0.02 ppm of copper before the amine was distilled from EDTA. In all, we do not believe the reported C-N bond formations[6] are catalyzed by $MnCl_2$, but most likely minute amounts of copper in the reagents and the solvent are responsible for the observed transformations.

The reaction in Scheme 4 has also been published with 10% of $CoCl_2$•$6H_2O$ and 20% of *N*,*N*'-dimethylethylenediamine instead of $MnCl_2$ and *trans*-1,2-diaminocyclohexane where a 75% yield of 1-(*m*-tolyl)-1H-pyrazole was obtained.[17] In our hands and with purified reactants the yield was only 6% which also in this case indicates that the added cobalt salt is not the true catalyst for the reported transformation.

Conclusions

In summary, the substrate scope of the $MnCl_2$-catalyzed coupling between aryl halides and Grignard reagents has been extended to methyl-substituted aryl iodides by performing the reaction a microwave oven. An aryl radical was identified by a radical clock experiment and the coupling is therefore also in this case believed to proceed by a $S_{RN}1$ mechanism. The role of $MnCl_2$ is most likely to react with the Grignard reagent to provide a softer nucleophile which can also serve as a one-electron donor. The mechanistic information caused suspicion about two previously published manganese-catalyzed cross-coupling reactions. In fact, control experiments revealed that manganese(II) salts are not able to catalyze the coupling between aryl halides and organostannanes/amines. The results illustrate the importance of mechanistic experiments as well as analyses for trace metals when developing new metal catalysts for known catalytic transformations.

Experimental Section

General: All the reactions were performed in a Biotage microwave reactor and monitored by gas chromatography on a Shimadzu GCMS-QP2010S instrument fitted with an Equity 5, 30 m × 0.25 mm × 0.25 μm column. Flash column chromatography separations were performed on silica gel 60 (40 – 63 μm). NMR spectra were recorded on a Bruker Ascend 400 spectrometer. Chemical shifts were measured relative to the signals of residual $CHCl_3$ (δ_H = 7.26 ppm) and $CDCl_3$ (δ_C = 77.16 ppm). Analyses for trace metals by ICP-MS was performed by ALS Denmark A/S.

General Procedure for Cross Coupling: $MnCl_2$ (25 mg, 0.2 mmol) was placed in a predried microwave vial (with a liquid volume allowance between 0.5 mL and 2 mL) equipped with a magnetic stirrer and then sealed with a rubber septum. The vial was evacuated and refilled three times with nitrogen through a syringe. The aryl halide (2 mmol) and decane (1 mmol, internal standard) were placed in the vial followed by addition of 3 M phenylmagnesium bromide (4 mmol) in diethyl ether under a flow of nitrogen. The reaction vial was sealed with a cap and placed in the microwave reactor at 120 °C for 5 h. The mixture was quenched with a saturated solution of ammonium chloride. The phases were separated and the aqueous phase extracted with diethyl ether (3 x 5 mL). The combined organic phases were dried over Na_2SO_4, filtered and evaporated *in vacuo* to give the crude product, which were purified by flash chromatography eluting with pentane or pentane containing 0.5 – 10% EtOAc.

4-Methyl-1,1'-biphenyl:[18] Table 2, Entries 1 and 2. Prepared from *p*-iodotoluene and phenylmagnesium bromide according to the general procedure. The residue was purified by flash column chromatography eluting with pentane to yield a mixture of biphenyl and 4-methyl-1,1'-biphenyl. The yield of the latter was determined by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.49 (m, 2 H), 7.42–7.32 (m, 4 H), 7.28–7.21 (m, 1 H), 7.18–7.14 (m, 2 H), 2.31 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.3, 138.5, 137.1, 129.6, 128.8, 127.1, 127.1, 21.2 ppm. MS: *m*/*z* = 168.00 $[M]^+$.

3-Methyl-1,1'-biphenyl:[18] Table 2, Entry 3. Prepared from *m*-iodotoluene and phenylmagnesium bromide according to the general procedure. The residue was purified by flash column chromatography eluting with pentane to yield a mixture of biphenyl and 3-methyl-1,1'-biphenyl. The yield of the latter was determined by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62–7.59 (m, 2 H), 7.48–7.33 (m, 6 H), 7.19–7.17 (m, 1 H), 2.44 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.5, 141.4, 138.5, 128.8, 128.8, 128.1, 127.3, 124.4, 21.7 ppm. MS: *m*/*z* = 168.05 $[M]^+$.

2-Methyl-1,1'-biphenyl:[19] Table 2, Entry 4. Prepared from *o*-iodotoluene and phenylmagnesium bromide according to the general procedure. The residue was purified by flash column chromatography eluting with pentane to yield a mixture of biphenyl and 2-methyl-1,1'-biphenyl. The yield of the latter was determined by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.40 (m, 2 H), 7.37–7.32 (m, 3 H), 7.28–7.23 (m, 4 H), 2.28 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.1, 142.1, 135.5, 130.4, 129.9, 129.3, 128.2, 127.3, 126.9, 125.9, 20.6 ppm. MS: *m*/*z* = 168.05 $[M]^+$.

3,4-Dimethyl-1,1'-biphenyl:[20] Table 2, Entry 5. Prepared from 1-iodo-3,4-dimethylbenzene and phenylmagnesium bromide according to the general procedure. The residue was purified by flash column chromatography eluting with pentane to yield the desired product as a colorless oil (75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.58 (m, 2 H), 7.45–7.39 (m, 3 H), 7.36–7.31 (m, 2 H), 7.22 (d, *J* = 7.7 Hz, 1 H), 2.35 (s, 3 H), 2.32 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.4, 139.0, 137.0, 135.8, 130.2, 128.8, 128.6, 127.1, 127.0, 124.6, 20.1, 19.6 ppm. MS: *m*/*z* = 182.00 $[M]^+$.

3,5-Dimethyl-1,1'-biphenyl:[18] Table 2, Entry 6. Prepared from 1-iodo-3,5-dimethylbenzene and phenylmagnesium bromide according to the general procedure. The residue was purified by flash column chromatography eluting with pentane to yield a mixture of biphenyl and 3,5-methyl-1,1'-biphenyl. The yield of the cross-coupling product was determined by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.59 (m, 2 H), 7.49–7.43 (m, 2 H), 7.39–7.33 (m, 2 H), 7.24 (br s, 1 H), 7.24 (br s, 1 H), 2.41 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.6, 141.4, 138.4, 129.0, 128.8, 127.3, 127.2, 125.2, 21.6 ppm. MS: *m*/*z* = 182.00 $[M]^+$.

3-Methoxy-1,1'-biphenyl:[19] Table 2, Entry 7. Prepared from *m*-iodoanisole and phenylmagnesium bromide according to the general procedure. The residue was purified by flash column chromatography eluting with pentane/EtOAc (10:0.05) to yield the desired product as white solid (26%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.58 (m, 2 H), 7.46–7.42 (m, 2 H), 7.38–7.33 (m, 2 H), 7.20–7.18 (m, 1 H), 7.14–7.13 (m, 1 H), 6.92–6.89 (m, 1 H), 3.87 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1, 142.9, 141.3, 128.9, 128.9, 127.6, 127.3, 119.8, 113.0, 112.8, 55.5 ppm. MS: *m*/*z* = 184.00 $[M]^+$.

4-Methoxy-1,1'-biphenyl:[18] Table 2, Entry 8. Prepared from *p*-iodoanisole and phenylmagnesium bromide according to the general procedure. The residue was purified by flash column chromatography, eluting with pentane/EtOAc (10:0.05) to yield the desired product as white solid (23%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.52 (m, 4 H), 7.44–7.40 (m, 2 H), 7.33–7.28 (m, 1 H), 7.00–6.97 (m, 2 H), 3.86 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 141.0, 133.9, 128.9, 128.3, 126.9, 126.8, 114.3, 55.5 ppm. MS: *m*/*z* = 184.00 $[M]^+$.

***N*,*N*-Dimethyl-[1,1'-biphenyl]-3-amine:**[21] Table 2, Entry 9. Prepared from 3-bromo-*N*,*N*-dimethylaniline and phenylmagnesium bromide according to the general procedure. The residue was purified by flash column chromatography eluting with pentane/EtOAc (10:1) to yield the desired product as colorless oil (33%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.61 (m, 2 H), 7.47–7.44 (m, 2 H), 7.38–7.32 (m, 2 H), 7.00–6.97 (m, 2 H), 6.80–6.77 (m, 1 H), 3.03 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.1, 142.4, 142.4, 129.5, 128.7, 127.5, 127.2, 116.1, 111.8, 111.8, 40.9 ppm. MS: *m*/*z* = 197.05 $[M]^+$.

***N*,*N*-Dimethyl-[1,1'-biphenyl]-4-amine:**[22] Table 2, Entry 10. Prepared from 4-bromo-*N*,*N*-dimethylaniline and phenylmagnesium bromide according to the general procedure. The residue was purified by flash column chromatography eluting with pentane/EtOAc (10:1) to yield the desired product as white solid (28%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.52 (m, 4 H), 7.43–7.39 (m, 2 H), 7.29–7.25 (m, 1 H), 6.84–6.82 (m, 2 H), 3.01 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.1, 141.3, 128.8, 127.9, 126.4, 126.1, 113.0, 40.8 ppm. MS: *m*/*z* = 197.00 $[M]^+$.

Radical Clock Experiment in Scheme 1: Commercially available 4-(2-bromophenyl)-but-1-ene was treated with $MnCl_2$ and phenylmagnesium bromide as described above in the general procedure to afford an inseparable mixture of compounds **1** – **3** and **5** which were characterized by NMR and the yield determined with an internal standard. In addition, compound **4** was isolated as a mixture with biphenyl and again characterized by NMR.

1-Methylindan (1):[23] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.12 (m, 4 H), 3.20 (sextet, *J* = 7.2 Hz, 1 H), 3.02–2.79 (m, 2 H), 2.36–2.28 (m, 1 H), 1.66–1.57 (m, 1 H), 1.31 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.9, 144.0, 128.4, 126.2, 124.5, 123.3, 39.6, 34.9, 31.6, 20.0 ppm. MS: *m*/*z* = 132.05 $[M]^+$.

1-Methyleneindan (2):[24] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.12 (m, 4 H), 5.47 (t, *J* = 2.6 Hz, 1 H), 5.09–5.08 (m, 1 H), 3.02–2.98 (m, 2 H), 2.93–2.79 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.7, 146.9, 141.2, 128.4, 126.5, 125.5, 120.7, 102.6, 31.3, 30.2 ppm.

3-Methyl-1*H*-indene (3):[24] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.12 (m, 4 H), 6.22–6.21 (m, 1 H), 3.34–3.33 (m, 2 H), 2.20–2.18 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.2, 144.5, 140.1, 128.9, 126.2, 124.6, 123.7, 119.0, 37.8, 13.2 ppm.

2-(But-3-en-1-yl)-1,1'-biphenyl (4):[25] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.24 (m, 9 H), 5.73 (ddt, *J* = 16.9,10.2, 6.6 Hz, 1 H), 4.94 (q, *J* = 1.7 Hz, 1 H), 4.91–4.89 (m, 1 H), 2.72–2.68 (m, 2 H), 2.26–2.20 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.1, 142.0, 139.4, 138.3, 130.2, 129.3, 128.2, 127.5, 126.9, 125.9, 114.8, 35.3, 32.7 ppm. MS: *m*/*z* = 208.00 $[M]^+$.

4-Phenylbut-1-ene (5):[26] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.12 (m, 5 H), 5.88 (ddt, *J* = 16.9,10.2, 6.6 Hz, 1 H), 5.05–5.04 (m, 1 H), 5.00 (dd, *J* = 10.2, 1.6 Hz, 1 H), 2.75–2.71 (m, 2 H), 2.42–2.37 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.0, 138.2, 128.6, 126.2, 125.9, 115.0, 35.7, 35.5 ppm. MS: *m*/*z* = 132.05 $[M]^+$.

Acknowledgements

We thank the Danish Council for Independent Research – Technology and Production Sciences for financial support (grant 1335-00153).

Keywords: Cross-coupling • Grignard reagent • Manganese • Radical reactions • Trace analysis

[1] A. B. Santamaria, S. I. Sulsky, *J. Toxicol. Environ. Health A* **2010**, *73*, 128–155.

[2] (a) J. R. Carney, B. R. Dillon, S. P. Thomas, *Eur. J. Org. Chem.* **2016**, 3912–3929. (b) W. Liu, L. Ackermann, *ACS Catal.* **2016**, *6*, 3743–3752. (c) D. A. Valyaev, G. Lavigne, N. Lugan, *Coord. Chem. Rev.* **2016**, *308*, 191–235.

[3] (a) G. Antonacci, A. Ahlburg, P. Fristrup, P.-O. Norrby, R. Madsen, *Eur. J. Org. Chem.* (2017) DOI: 10.1002/ejoc.201700981. (b) G. Cahiez, O. Gager, F. Lecomte, *Org. Lett.* **2008**, *10*, 5255–5256. (c) M. Rueping, W. Ieawsuwan, *Synlett* **2007**, 247–250. (d) G. Cahiez, F. Lepifre, P. Ramiandrasoa, *Synthesis* **1999**, 2138–2144. (e) M. Alami, P. Ramiandrasoa, G. Cahiez, *Synlett* **1998**, 325–327.

[4] S.-K. Kang, J.-S. Kim, S.-C. Choi, *J. Org. Chem.* **1997**, *62*, 4208–4209.

[5] (a) J. Qiao, W. Zhu, G. Zhuo, H. Zhou, X. Jiang, *Chin. J. Catal.* **2008**, *29*, 209–211. (b) S. Iyer, V. V. Thakur, *J. Mol. Catal. A: Chem.* **2000**, *157*, 275–278.

[6] (a) F.-F. Yong, Y.-C. Teo, *Synlett* **2012**, 2106–2110. (b) F.-F. Yong, Y.-C. Teo, *Tetrahedron Lett.* **2010**, *51*, 3910–3912. (c) Y.-C. Teo, F.-F. Yong, C.-Y. Poh, Y.-K. Yan, G.-L. Chua, *Chem. Commun.* **2009**, 6258–6260.

[7] I. Thomé, A. Nijs, C. Bolm, *Chem. Soc. Rev.* **2012**, *41*, 979–987.

[8] (a) R. B. Bedford, M. Nakamura, N. J. Gower, M. F. Haddow, M. A. Hall, M. Huwe, T. Hashimoto, R. A. Okopie, *Tetrahedron Lett.* **2009**, *50*, 6110–6111. (b) S. L. Buchwald, C. Bolm, *Angew. Chem. Int. Ed.* **2009**, *48*, 5586–5587; *Angew. Chem.* **2009**, *121*, 5694–5695. (c) H. Plenio, *Angew. Chem. Int. Ed.* **2008**, *47*, 6954–6956; *Angew. Chem.* **2008**, *120*, 7060–7063. (d) R. K. Arvela, N. E. Leadbeater, M. S. Sangi, V. A. Williams, P. Granados, R. D. Singer, *J. Org. Chem.* **2005**, *70*, 161–168.

[9] J. Tammiku-Taul, P. Burk, A. Tuulmets, *J. Phys. Chem. A* **2004**, *108*, 133–139.

[10] Recently, alkyl radicals were trapped in radical clock experiments for the $MnBr_2$-catalyzed borylation of alkyl chlorides, see: T. C. Atack, S. P. Cook, *J. Am. Chem. Soc.* **2016**, *138*, 6139–6142.

[11] C. Ha, J. H. Horner, M. Newcomb, T. R. Varick, B. R. Arnold, J. Lusztyk, *J. Org. Chem.* **1993**, *58*, 1194–1198.

[12] J. Nakao, R. Inoue, H. Shinokubo, K. Oshima, *J. Org. Chem.* **1997**, *62*, 1910–1911.

[13] G. Cahiez, C. Duplais, J. Buendia, *Chem. Rev.* **2009**, *109*, 1434–1476.

[14] N. Uchiyama, E. Shirakawa, T. Hayashi, *Chem. Commun.* **2013**, *49*, 364–366.

[15] F. De Vleeschouwer, V. Van Speybroeck, M. Waroquier, P. Geerlings, F. De Proft, *Org. Lett.* **2007**, *9*, 2721–2724.

[16] P.-F. Larsson, A. Correa, M. Carril, P.-O. Norrby, C. Bolm, *Angew. Chem. Int. Ed.* **2009**, *48*, 5691–5693; *Angew. Chem.* **2009**, *121*, 5801–5803.

[17] Y.-C. Teo, *Adv. Synth. Catal.* **2009**, *351*, 720–724.

[18] H. Yang, L. Zhang, L. Jiao, *Chem. Eur. J.* **2017**, *23*, 65–69.
[19] Q.-X. Liu, K.-Q. Cai, Z.-X. Zhao, *RSC Adv.* **2015**, *5*, 85568–85578.
[20] F. Gaviña, A. M. Costero, A. M. González, *J. Org. Chem.* **1990**, *55*, 2060–2063.
[21] D. Heijnen, J.-B. Gualtierotti, V. Hornillos, B. L. Feringa, *Chem. Eur. J.* **2016**, *22*, 3991–3995.
[22] A. Ohtsuki, K. Yanagisawa, T. Furukawa, M. Tobisu, N. Chatani, *J. Org. Chem.* **2016**, *81*, 9409–9414.
[23] W. F. Bailey, M. J. Mealy, *J. Am. Chem. Soc.* **2000**, *122*, 6787–6788.
[24] M. R. Friedfeld, M. Shevlin, G. W. Margulieux, L.-C. Campeau, P. S. Chirik, *J. Am. Chem. Soc.* **2016**, *138*, 3314–3324.
[25] N. Uchiyama, E. Shirakawa, T. Hayashi, *Chem. Commun.* **2013**, *49*, 364–366.
[26] A. Chatterjee, S. H. H. Eliasson, K. W. Törnroos, V. R. Jensen, *ACS Catal.* **2016**, *6*, 7784–7789.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

Text for Table of Contents

((Insert TOC Graphic here: max. width: 5.5 cm; max. height: 5.0 cm; NOTE: the final letter height should not be less than 2 mm.))

Key Topic*

*Author(s), Corresponding Author(s)**

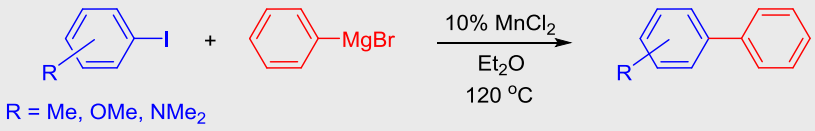
Page No. – Page No.

Title

*one or two words that highlight the emphasis of the paper or the field of the study

Layout 2:

FULL PAPER



Manganese Catalysis

*Carola Santilli, Somayyeh Sarvi Beigbaghlou, Andreas Ahlburg, Giuseppe Antonacci, Peter Fristrup, Per-Ola Norrby, Robert Madsen**

Page No. – Page No.

The Manganese-Catalyzed Cross-Coupling Reaction and the Influence of Trace Metals

The substrate scope of the $MnCl_2$-catalyzed coupling between aryl halides and Grignard reagents has been extended to unactivated halides by performing the reaction in a microwave oven. An aryl radical was identified as an intermediate leading to the proposal of an $S_{RN}1$ pathway. Two previously published cross coupling reactions with manganese catalysts were revisited and found impossible to reproduce without the assistance of small amounts of palladium or copper.